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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/766,057	01/28/2004	Roy H. Larsen	50147/003002	2306

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EXAMINER	
PERREIRA, MELISSA JEAN	
ART UNIT	PAPER NUMBER
1618	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/07/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/766,057	LARSEN ET AL.	
	Examiner	Art Unit	
	Melissa Perreira	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 January 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *18 and 25-35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *18 and 25-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 18 and 25-35 are pending in the application. Claims 1-17 and 19-24 were cancelled and claims 25-35 were newly added in the response filed 1/8/07.

Any rejections from previous office actions that have not been reiterate in this office action are obviated.

New Ground of Rejection Necessitated by the Amendment to the Claims

Claim Rejections - 35 USC § 102

1. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

2. Claims 31 and 35 are rejected under 35 U.S.C. 102(b) as being anticipated by Niswender (US 4,336,185).

3. Niswender (US 4,336,185) teaches of a receptor binding conjugate comprising three components, 1.) an antibody fragment, such as a tyrosine, 2.) a radionuclide or radionuclides and 3.) folic acid and salts, esters, and amides thereof (column 5, examples 3 and 4) and the methods of making the conjugates. The intermediate folate thyroglobulin conjugate is also disclosed albeit without the radionuclide coupled to the folate-antibody conjugate (column 4, lines 62+).

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 18 and 25-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sinkule et al. (EP 282057) in view of Wedeking et al. (US 6,093,382).

6. Sinkule et al. (EP 282057) discloses a receptor binding conjugate comprising three components, 1.) a monoclonal antibody (column 2, lines 30-31), 2.) a radionuclide and 3.) a chemotherapeutic agent, such as folate or analogues thereof (abstract; column 2, lines 11-14 and 29-30) or multiples thereof (column 4, lines 18-28) which are prepared by attaching a radionuclide to a conjugate comprising an antibody and a therapeutic agent (column 6, lines 22-25). The antibody may be a monoclonal or polyclonal or variations thereof used for a wide variety of target antigens (column 3, lines 56+; column 4, lines 9-12). Various radionuclides are disclosed, such as ^{125}I, ^{99m}Tc or others encompassed by the instant claims (column 3, lines 39+) and may be bound to the antibody-therapeutic agent conjugate via a chelating compound (column 17, lines 5-17). Targeting antibodies may be included in the conjugate to target the conjugate to a desired tumor cell for uptake via administration to a mammalian host (column 5, lines 10-12 and 22+; column 6, lines 26-30). The antibodies disclosed for conjugating to a radionuclide-chemotherapeutic agent include IgG, such as 443A6

which recognize a 40k dalton epithelial antigen found on human breast adenocarcinomas (column 8, lines 33-39; example 3). The therapeutic agent chosen for use will vary according to the nature of the disease to be treated and the type of target cells to be eradicated *in vivo* within human or mammalian host (column 3, lines 5-12; column 5, lines 22-25). The conjugate can be administered by any conventional method, such as intravenously and the pharmaceutical agents may be in various pharmaceutical compositions with various combinations of materials therefore. The method of preparing the folic acid derivative-antibody bond involves conversion of the folic acid derivative to the activated ester (mixed anhydride) with acetic anhydride (column 8, lines 40-44). Sinkule et al. (EP 282057) does not disclose the conjugation of folic acid (folate).

7. Wedeking et al. (US 6,093,382) discloses the gadolinium-folate (folic acid) conjugates (column 7, lines 21-28; column 8, line 56; column 10, lines 18-25) that are used to target the radionuclide to tumor cells via FBP (folate binding protein) and their methods or preparation and use (column 6, lines 28+; column 7, lines 48-50). The compound of column 51-52 contains multiple folates (folic acid) conjugated to a radionuclide chelate capable of binding gadolinium. The method of targeting a gadolinium-folate (folic acid) conjugate to a cell involves administering to a mammal the conjugate and monitoring the biodistribution (column 68, lines 31+; example 17). Also disclosed is that cellular uptake of folate into cells is via a high affinity membrane bound folate-binding protein and it is transported into the cell and diffuses into the cytoplasm where it is rapidly coupled to one or more glutamic acid residues thus slowing diffusion

out of the cell (column 3, lines 3-24). Due to the overexpression of folate binding protein in cancer cells, such as ovarian cancer cells (column 3, lines 34-35; column 4, lines 42-43) it would be obvious that the targeting of a radionuclide would be enhanced by conjugation to folic acid (column 5, lines 1-7).

8. At the time of the invention it would have been obvious to one ordinarily skilled in the art to substitute a folic acid (folate) as disclosed by Wedeking et al. for a folic acid (folate) derivative as disclosed by Sinkule et al. as it is can be utilized to target a conjugate into a cell with enhanced affinity (see above). The folic acid is also a known vitamin which can provide nutrients to a subject. It is obvious to substitute variants of similar structure in order to generate the most efficient and effective diagnostic and/or therapeutic agent.

9. Claims 18,25-28 and 30-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Niswender (US 4,336,185) in view of Goldenberg et al. (US 5,698,178) and Wedeking et al. (US 6,093,382).

10. Niswender (US 4,336,185) discloses a receptor binding conjugate comprising three components, 1.) an antibody fragment, such as a tyrosine, 2.) a radionuclide or radionuclides and 3.) folic acid and salts, esters, and amides thereof (column 5, examples 3 and 4) and the methods of making the conjugates. The intermediate folate thyroglobulin conjugate is also disclosed albeit without the radionuclide coupled to the folate-antibody conjugate (column 4, lines 62+). Niswender does not disclose the

method of selectively targeting the antibody fragment-folate-radionuclide conjugates to malignant cells.

11. Goldenberg et al. (US 5,698,178) discloses the method of selectively targeting diagnostic and therapeutic agents to multidrug resistant cells via administration of receptor binding conjugates (column 4, lines 1-4; column 5, line 56; column 23, lines 1-3). The receptor binding conjugates comprise various antibodies and at least one diagnostic or therapeutic agent (abstract, column 4, lines 8-26). The diagnostic and therapeutic agents include radionuclides, such as ^{25}I, ^{99m}Tc, etc. (column 20, lines 39-53) and cancer chemotherapeutic drugs, such as folic acid analogues (column 4, lines 44 and 55; column 23, lines 11+ and lines 55-57). Humanized antibodies may be used as an equivalent to other antibodies for targeting a desired site and that the use of humanized antibodies obviates potential problems associated with the immunogenicity of murine constant regions (column 10, line 17+; column 12, lines 4-13). Antibodies that may be used as the targeting antibody which provides for the clearance of a nontargeted circulating radiolabeled antibody are IgG and IgM (column 20, lines 54+). The method of preparing the conjugates involves coupling an antibody to a diagnostic or therapeutic agent (column 15, lines 43-45; example 4). Goldenberg et al. (US 5,698,178) does not disclose the conjugation of folic acid (folate).

12. Wedeking et al. (US 6,093,382) discloses the gadolinium-folate (folic acid) conjugates (column 7, lines 21-28; column 8, line 56; column 10, lines 18-25) that are used to target the radionuclide to tumor cells via FBP (folate binding protein) and their methods or preparation and use as well as that listed above.

13. At the time of the invention it would have been obvious to one ordinarily skilled in the art to it would have been obvious to utilize an antibody (fragment)-folate-radionuclide conjugate for the method of targeting a radionuclide to a malignant cell as Goldenberg et al. discloses a targeting the antibody-radionuclide or antibody-folic acid analog to tumor cells and Wedeking et al. specifically discloses the targeting of gadolinium-folate (folic acid) conjugates to ovarian cancer cells. Folate has a high cellular uptake cells via a high affinity membrane bound folate-binding protein and it is transported into the cell and diffuses into the cytoplasm where it is rapidly coupled to one or more glutamic acid residues thus slowing diffusion out of the cell. Due to the overexpression of folate binding protein in cancer cells, such as ovarian cancer cells it would be obvious that the targeting of a radionuclide would be enhanced by conjugation to folic acid (as stated above).

Double Patenting

14. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to

be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

15. Claims 18,25-28 and 31-35 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-6 of U.S. Patent No. US 6,740,304B2. Although the conflicting claims are not identical, they are not patentably distinct from each other because the method of delivering therapeutic radiation to a patient with a malignant cell of US 6,740,304B2 encompasses the method of targeting a radionuclide to a malignant cell within a subject of the instant claims. The methods involve identical conjugates comprising a human IgG or IgM antibody, folate (not excluding multiple folates) and a radionuclide. The species of administration techniques, such as intravenously of US 6,740,304B2 anticipates the genus of administration of the instant claims. The cells to target or deliver the radionuclide are brain, cervical, ovarian, or breast and the species of radionuclides, such as ^{125}I of US 6,740,304B2 anticipates the genus or radionuclide of the instant claims.

Conclusion

No claims are allowed at this time.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Melissa Perreira whose telephone number is 571-272-1354. The examiner can normally be reached on 9am-5pm M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mike Hartley can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

MP
February 21, 2007

MICHAEL G. HARTLEY
SUPERVISORY PATENT EXAMINER